REMARKS

Claims 21-44 are pending in the application. Claims 21, 22, and 31-44 are withdrawn as being drawn to non-elected inventions. Claims 23-30 are under consideration. Claims 21 and 27 have been amended to further clarify the intended subject matter of the claimed invention. Entry of these amendments is respectfully requested. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Comments Regarding Restriction Requirement

Applicants affirm the election with traverse of Group 28, which corresponds to claims 23-30 drawn to polynucleotides.

Applicants reiterate the request that the Examiner withdraw the Restriction Requirement at least with respect to claims 21, 22, 34, and 35 of Group 11, and examine those claims together with the elected polynucleotide claims of Group 28.

The rules under MPEP section 1893.03(d) require the Examiner to apply the Unity of Invention standard PCT Rule 13.2 instead of U.S. restriction/election of species practice in national stage applications, such as the instant application filed under 35 U.S.C. 371. Applicants believe unity of invention exists for claims drawn to the polypeptide sequence of SEQ ID NO:1 (*i.e.*, claims 21, 22, 34, and 35) and claims drawn to the elected polynucleotide sequence of SEQ ID NO:31 which encodes SEQ ID NO:12 (*i.e.*, claims 23-30) based on the rules concerning unity of invention under the Patent Cooperation Treaty. The Administrative Instructions Under The Patent Cooperation Treaty, Annex B, Unity of Invention, Part 2, "Examples Concerning Unity of Invention" provide the following guidelines with regard to unity of invention between a protein and the polynucleotide that encodes it:

> *Example 17*
> Claim 1: Protein X.
> Claim 2: DNA sequence encoding protein X.
> Expression of the DNA sequence in a host results in the production of a protein which is determined by the DNA sequence. The protein and the DNA sequence exhibit corresponding special technical features. Unity between claims 1 and 2 is accepted.

Applicants submit that Example 17 does apply to the claims of the instant application, since the polynucleotide of SEQ ID NO:31 does encode the polypeptide of SEQ ID NO:12. In particular, claims 21 and 23 meet the unity of invention standard. Claim 23 recites an isolated

polynucleotide encoding a polypeptide of claim 21. Unity of invention is accepted between a protein and the polynucleotide that encodes it. The refusal to examine claims drawn to polynucleotides and polypeptides together on the grounds that "the polynucleotide is structurally distinct from the polypeptide" is improper.

Rejoinder of method claims upon allowance of product claims under U.S. practice

The Examiner is reminded that claims 31-33, 38, and 39, drawn to methods of using the elected polynucleotides of Group 28 should be rejoined per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants request that claims 31-33, 38, and 39 be rejoined and examined upon allowance of the claims drawn to the polynucleotides of Group 28.

Objection to the Specification

Hyperlinks

The Examiner objected to the presence of references to hyperlinks and/or other forms of browser-executable code in the specification (Office Action, page 3). Applicants did not intend to have active links in the specification, nor to incorporate the subject matter of websites by reference to such hyperlinks. Applicants have amended the specification to remove active hyperlinks and therefore respectfully request that the Examiner withdraw the objection to the specification.

Title

As mentioned above, Applicants believe that the claims drawn to the polypeptides of the invention, according to the unity of invention standard, should be examined with the elected claims drawn to the polynucleotides currently under examination. Applicants request reconsideration and believe amending the title at this time would be premature.

Priority Claim

The priority claim has been amended to indicate that the instant application is the National Stage application of PCT/US99/24511. Therefore, withdrawal of the objection to the specification is respectfully requested.

Objections to the claims

Claims 23-29 are objected to because of their dependence from non-elected claims 21 and 22. As mentioned above, Applicants believe that the claims drawn to the polypeptides of the invention, according to the unity of invention standard, should be examined with the elected claims drawn to the polynucleotides currently under examination. Applicants request reconsideration and believe amending the claims at this time would be premature.

Utility Rejections under 35 U.S.C. §101 and §112, First Paragraph

Claims 23-30 have been rejected under 35 U.S.C. §101 and §112, first paragraph, because the claimed invention allegedly "is not supported by either a specific and substantial asserted utility or a well-established utility" (Office Action, page 4). These rejections are traversed.

The rejection of claims 23-30 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in gastrointestinal, nervous system, and reproductive tissues (Specification at Table 3). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions.

Applicants submit with this paper the Declaration of Dr. Tod Bedilion[1] describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

[1]The Bedilion Declaration is submitted herewith in unexecuted form. The executed Declaration will be submitted to the Patent office as soon it is available.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would appreciate that cDNA microarrays that contained the SEQ ID NO:12-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cancer and other disorders of cell proliferation for such purposes as evaluating their efficacy and toxicity.

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of

> achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the

Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. The utilities we disclose in our specifications are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

Our sequence inventions meet all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed inventions known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the inventions disclosed in the patent applications' specification. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of our sequence inventions for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed inventions have specific, substantial, real-world utility by virtue of their use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses have are explained in detail to the USPTO, and the substance of these arguments has not rebutted by the USPTO. There is no dispute that the claimed inventions are in fact useful tools in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

It clear that a person skilled in the art reading our patent applications as of their filing dates would have understood those applications to disclose the claimed polynucleotides to be useful for a number of gene expression monitoring applications, *e.g.*, as highly specific probes for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. References and other data submitted in these applications concern the use of the claimed polynucleotide in cDNA microarrays of the type first

developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications.[2]

In connection with our explanations, we demonstrated that our specifications would have led a person skilled in the art on the various priority dates who was using gene expression monitoring in connection with working on developing new drugs for the treatment of various diseases to conclude that a cDNA microarray that contained all of the various polypeptide-encoding polynucleotides would be a highly useful tool, and to request specifically that any cDNA microarray that was being used for such purposes contain each and every specific polypepide-encoding polynucleotides we claimed. Thus, persons skilled in the art would have appreciated on our filing dates that a cDNA microarray that contained each of the claimed polypeptide-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain these polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating various diseases for such purposes as evaluating their efficacy and toxicity.

In support of those statements, we provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-filing date publications showing the state of the art on that date. Even these explanations were shown to not be all-inclusive. For example, with respect to toxicity evaluations, we presented evidence that persons skilled in the art who were working on drug development on our priority dates (and for several years prior to them) without any doubt have appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the each application clearly included using differential gene expression analyses in toxicity studies.

Thus, we established on the record that persons skilled in the art reading our patent applications at the time they were filed would have wanted their cDNA microarray to have the various polypeptide- encoding polynucleotide probes we claimed because a microarray that

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[2]For example, we explained why persons skilled in the art would also appreciate, based on our specifications, that the claimed polynucleotides would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the microarray technology.

contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to our priority dates. This, by itself, provided more than sufficient reason to compel the conclusion that our applications disclosed to persons skilled in the art at the time of their filing substantial, specific and credible real-world utilities for our claimed polynucleotides.

Never did the USPTO address the fact that, as described in our applications, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed inventions are not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that our claimed polynucleotides are known to be expressed, their utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

Though we need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating various diseases, In particular where our patent applications stated explicitly that the claimed polynucleotide is known to be expressed both in normal cells as well as cancerous and immortalized cells and expresses a protein that is a member of a particular class of proteins known to be associated with specific diseases, there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of

ordinary skill in the art can derive more information about a potential drug candidate or potential toxin with the claimed invention than without it.

We further showed that a number of pre-priority date publications confirmed and further established the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time these applications were filed. Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognized the patentable utility of the cDNA technology developed in the early to mid-1990s. As we explained, the Brown '522 patent further teaches that the"[m]croarrays of immobilized nucleic acid sequences prepared in accordance with the invention can be used in numerous genetic applications, including monitoring of gene expression applications." The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies.

Literature reviews published after the filing of our rejected applications describing the state of the art further confirm our claimed inventions' utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal

> . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999).

In another article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (emphasis added).

B. The use of nucleic acids coding for proteins expressed by humans (as well as research organisms) as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected

control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the USPTO has failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the rejections should be overturned on appeal regardless of their merit.

C. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, the utility of many of our claimed polynucleotides can be imputed based on the disclosed relationship between the polypeptide it encodes and another

polypeptide of unquestioned utility. In the case where such homology has been asserted as an independent basis for utility, the two polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the art would recognize more than a reasonable probability that the polypeptide encoded for by the claimed invention has utility similar to the known polypeptide. Patent applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed in most cases, and readily apparent from the patent application, that the polypeptide encoded for by the claimed polynucleotide shares significant sequence identity with the reference polypeptide. We have submitted references which disclose that the percent identity disclosed is more than enough homology to demonstrate a reasonable probability that the utility of the reference polypeptide can be imputed to the claimed invention (through the polypeptide it encodes). It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the polypeptide encoded for by our claimed polynucleotides is related to the reference polypeptides is, accordingly, very high.

The USPTO must accept the applicants' demonstration that the homology between the polypeptide encoded for by the claimed invention and the reference polypeptide demonstrates utility by a reasonable probability unless they can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The USPTO has not provided sufficient evidence or sound scientific reasoning to the contrary in any of our cases.

While the USPTO has repeatedly cited literature identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in any particular case. Most important, none contradicts Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. Nor do they contradict our usual additional disclosure relating to additional evidence of similarity to the reference polypeptide, e.g., with respect to motif similarity, etc.. At most, these articles cited by the USPTO individually and together stand for the proposition that it is difficult to make predictions

about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

In other cases, in addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, it is undisputed that the claimed polynucleotide encodes for a protein that is a member of a specific protein family, and that that family of proteins includes proteins having specific function.

In those cases, the USPTO generally does not dispute any of the facts set forth. Neither does the USPTO dispute that, if a polynucleotide encodes for a protein that has a substantial, specific and credible utility, then it follows that the polynucleotide also has a substantial, specific and credible utility.

Under the Patent Law, the USPTO must accept the applicant's demonstration that the polypeptide encoded by the claimed invention is a member of a particular protein family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The USPTO does not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the USPTO provided any evidence that any member of a specific protein family, let alone a substantial number of those members, is not useful. In such circumstances, the only reasonable inference is that the polypeptide encoded by the claimed invention must be, like the other members of the asserted protein family, useful.

D. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates (see above). As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus our inventions adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase the claimed polynucleotide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra.*

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not specific, substantial, and credible utilities. (Office Action at pp. 4-9). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed

invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute

requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the oncogenic GTPase-activating protein family, the Examiner refused to impute the utility of the members of the oncogenic GTPase-activating protein family to PROAP. In the Office Action, the Patent Examiner takes the position that, unless Applicants can identify which particular biological function within the class of oncogenic GTPase-activating proteins is possessed by PROAP, utility cannot be imputed. To demonstrate utility by membership in the class of oncogenic GTPase-activating proteins, the Examiner would require that all oncogenic GTPase-activating proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses PROAP-12 as if the general class in which it is included is not the family of oncogenic GTPase-activating proteins, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a

substantial number of useless members, oncogenic GTPase-activating proteins do not. The oncogenic GTPase-activating protein family is sufficiently specific to rule out any reasonable possibility that PROAP-12 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the oncogenic GTPase-activating class of proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the PROAP encoded by the claimed polynucleotide is useful. It follows that the claimed polynucleotide also is useful.

Even if the Examiner's "common utility" criterion were correct – and it is not – the oncogenic GTPase-activating protein family would meet it. It is undisputed that known members of the oncogenic GTPase-activating protein family function in malignant transformation and tumorigenesis. A person of ordinary skill in the art need not know any more about how the claimed invention functions to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that unless Applicants can identify which particular biological function within the class of oncogenic GTPase-activating proteins is possessed by PROAP-12, utility cannot be imputed. The Examiner then goes on to assume that the only use for PROAP-12 absent knowledge as to how the oncogenic GTPase-activating protein actually works is further study of PROAP-12 itself.

Not so. As demonstrated by Applicants, knowledge that PROAP is an oncogenic GTPase-activating protein is more than sufficient to make it useful for the diagnosis and treatment of cancer and disorders of cell proliferation. Indeed, PROAP has been shown to be expressed in gastrointestinal, nervous system, and reproductive tissues and with tissues associated with cancer and inflammation. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. Because the uses of polynucleotides encoding PROAP-12 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

The PTO rejected the claims at issue on the ground that the use of an invention as a tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lacks utility (MPEP § 2107):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful, as well as DNA sequences used, for example, as markers.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include uses such as diagnostic assays (e.g., pages 41-46), chromosomal markers (e.g., page 45), ligand screening assays (e.g., pages 34 and 46), and drug screening (pages 43-46).

D. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

Moreover, the Tang '559 specification teaches that the PROAP protein having the amino acid sequence of SEQ ID NO:12 shares homology with known functional proteins. For example, SEQ ID NO:12 shares homology with the human Tre oncogene product (g37330) and contains a Rab GTPase-activating domain, characteristic of Tre-related oncogenic proteins (Specification, for example, at Table 2). A recent BLAST analysis of SEQ ID NO:12 shows that PROAP-12 is identical to the human PRC17 Rab GTPase-activating protein (g23452665), an oncogenic protein closely related to Tre (Please see the results of the BLAST search at Exhibit A and the enclosed reference of Pei et al (2002) Cancer Res. 62:5420-5424). The PRC17 oncogenic protein is known to be amplified in prostate cancer and may be useful as a cancer marker.

Because of the relationship between the PROAP protein of SEQ ID NO:12 and known functional proteins stated above, and because those known functional proteins are important in the types of regulatory mechanisms implicated in cancer and disorders of cell proliferation, persons skilled in the art on February 4, 1999 would have considered SEQ ID NO:12-encoding polynucleotides to be an important and valuable addition to a cDNA microarray for use in research into cancer and disorders of cell proliferation.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website

www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throw-away" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a

specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Rejection of Claim 27 Under 35 U.S.C. §101

The Examiner rejected claim 27 for allegedly being "directed to non-statutory subject matter" (Office Action, page 9). In particular the Examiner alleged that "[i]n the absence of the hand of man, the cell is considered non-statutory subject matter" (Office Action, page 9). In order to expedite prosecution, Applicants have amended claim 27, as suggested by the Examiner, to recite:

> 27. An isolated cell transformed with a recombinant polynucleotide of claim 26.

Therefore, Applicants respectfully request that the Examiner withdraw the utility rejection of claim 27 on this basis.

Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 23, 26-28, and 30 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not

> explicitly described in the specification, then the adequate description requirement is met. (footnotes omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:12 and SEQ ID NO:31 are specifically disclosed in the application (see, for example, pages 6-7). Variants of 12 and SEQ ID NO:31 are described, for example, at page 6, line 33 through page 7, line 6, and at page 7, lines 21-23. Incyte clones in which the nucleic acids encoding the human PROAP-12 were first identified and libraries from which those clones were isolated are described, for example, at Tables 1 and 4 of the Specification. Chemical and structural features of SEQ ID NO: 12 are described, for example, in Table 2. Given SEQ ID NO:12 and SEQ ID NO:31, one of ordinary skill in the art would recognize polynucleotide variants comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:31 and variants encoding polypeptides comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:12. Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

Additionally, the term "naturally occurring" is a well-known term in the art which Applicants intended to be used in such context. As such, no further definition of the term is necessary (MPEP 2163 IIA3(a)):

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

One of ordinary skill in the art would recognize that "***a naturally occurring amino acid sequence***" as recited in claim 21 is one which occurs in nature.

A. The Specification provides an adequate written description of the claimed "variants"of SEQ ID NO:12 and SEQ ID NO:31.

The Office Action has further asserted that the claims are not supported by an adequate written description because

> The general knowledge in the art concerning naturally occurring sequences does not provide any indication of how the structure of one sequence is representative of unknown sequences.
>
> (page 10 of the Office Action of August 1, 2003)

Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than functional characteristics. For example, the "variant language" of independent claim 30 recites chemical structure to define the claimed genus:

30. An isolated polynucleotide selected from the group consisting of: ...
b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:31...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:12. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the

recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to oncogenic GTPase-activating proteins related to the amino acid sequence of SEQ ID NO:12. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as oncogenic GTPase-activating proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:12. The "variant language" of the present claims recites, for example, polynucleotides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:12" (note that SEQ ID NO:12 has 549 amino acid residues). This variation is far less than that of all potential oncogenic GTPase-activating proteins related to SEQ ID NO:12, i.e., those oncogenic GTPase-activating proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:12.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of February 4, 1999. Much has happened in the development of recombinant DNA technology in the 22 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:12 and SEQ ID NO:31, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. The term "naturally occurring" is fully supported in the Specification as filed

Contrary to the Examiner's assertions, the Specification, as originally filed, provides adequate support for claiming polynucleotides encoding naturally occurring amino acid sequences having 90% sequence identity to SEQ ID NO:12. For example:

> "PROAP" refers to the amino acid sequences of substantially purified PROAP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.
> (Specification, page 9, line 34 through page 10, line 2)

Clearly, this definition of PROAP encompasses naturally occurring variants of SEQ ID NO:12 from different species. The Specification further describes the identification of variants of SEQ ID NO:31.

> In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding PROAP or closely related molecules may be used to identify nucleic acid sequences which encode PROAP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding PROAP, allelic variants, or related sequences.
> (Specification, at page 42, lines 6-12)
>
> In another embodiment of the invention, nucleic acid sequences encoding PROAP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)
> (Specification, at page 45, lines 10-16)
>
> Sequences complementary to the PROAP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring PROAP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of PROAP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the PROAP-encoding transcript.
> (Example VIII at page 53)
>
> Naturally occurring or recombinant PROAP is substantially purified by immunoaffinity chromatography using antibodies specific for PROAP. An immunoaffinity column is constructed by covalently coupling anti-PROAP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.
> (Example XIII at page 57)

In view of the foregoing evidence, Applicants submit that the rejection of claims 26, 29-31, and 34 on the grounds that there is no written support for "naturally-occurring" variants of SEQ ID NO:12 and SEQ ID NO:31 in the specification" is not only improper but also without merit.

5. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:12 or SEQ ID NO:31. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

Enablement rejections under 35 U.S.C. § 112, first paragraph

Claims 23, 26-28, and 30, are rejected for allegedly failing to meet the requirements of 35 U.S.C. § 112, first paragraph, on the grounds that the Specification does not provide an enabling disclosure commensurate in scope with the claims (Office Action pages 11-14). In particular, the Examiner asserts that "in view of the unpredictability in the art of protein chemistry as indicated above, and in view of the lack of guidance in the specification of the broadly claimed invention, it would require undue experimentation to practice the broadly claimed invention..." (Office Action, page 13-14). The Applicants traverse the rejection for at least the following reasons.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants submit that the disclosure amply enables the claimed invention. Given the sequences of SEQ ID NO:12 and SEQ ID NO:31, one of ordinary skill in the art could readily identify a polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:12 or a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:31, using well known methods of sequence analysis without any undue experimentation. For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, e.g., page 17, line 8 through page 18, line 10; page 30, lines 26-34; page 42, lines 6-12; page 45, lines 10-16; and Example VI at pages 51-52. Thus, one skilled in the art need not make and test vast numbers of polynucleotides. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides that already exist in nature. The skilled artisan would also know how to use the claimed polynucleotides, for example in expression profiling, disease diagnosis, or detection of related sequences as discussed above.

The specification also describes the expression vectors into which the claimed variants and fragments could be inserted, and the construction of fusion proteins (pages 26-30 and pages 53-54). The specification describes, for example, cell proliferation assays on page 54; binding assays to detect molecular interactions of "PROAP or biologically active fragments thereof" on page 57; and immunological methods for detecting and measuring PROAP on page 30, lines 16-25. These methods could be used to detect and characterize peptide variants and fragments of SEQ ID NO:12. Given this guidance, one of ordinary skill in the art would readily understand how to select and screen polynucleotides encoding variants or fragments of SEQ ID NO:12 without any undue experimentation.

To expedite prosecution, claim 21 c) has been amended to recite "a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:12, wherein said fragment induces cell proliferation." Applicants are amending the claim solely to obtain expeditious allowance of the instant application. Support for this amendment to claim 21 can be found in the specification, for example, in Table 2 which points out regions of homology between SEQ ID NO:12 and the Tre oncogene product (g37330), and at page 54, lines 7-15, which describes assays for measuring cell proliferation. By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include polypeptides or fragments having biological activities other than cell proliferation inducing activity.

The Examiner alleges that "there is no evidence identifying the biologically activity [sic] domain" (Office Action, page 13). This is untrue. In Table 2 of the specification, Applicants identified a Rab GTPase-activating domain likely to confer biological activity. The Examiner's attention is directed to Exhibit B, which shows the identification of a Tre/Bub2/Cdc16 (TBC)/Rab GTPase-activating protein (GAP) domain within SEQ ID NO:12, determined by a recent HMMER analysis. As discussed above in arguments presented concerning the utility of the claimed invention, a recent BLAST analysis shows that SEQ ID NO:12 is identical to the sequence of the PRC17 oncogene Rab GTPase-activating protein (g23452665), which is closely related to the TRE oncogene protein initially identified by Applicants as a homolog of the SEQ ID NO:12 polypeptide. Both PRC17 and TRE oncogene proteins contain GTPase-activating catalytic motifs and are known to stimulate the GTP hydrolysis activity of G proteins (See enclosed references of Pei et al. (2002) Cancer Res. 62:5420-5424; Lenka et al. (2002) J. Biol. Chem. 277:50996-51002; and Masuda-Robens et al. (2003) Mol. Cell. Biol. 23:2151-2161). Moreover, Pei et al. have confirmed that mutations in the GTPase-activating domain of the PRC17 protein abolish transforming activity.

The Examiner argues that "the method disclosed in the specification for the determination of the biological activity was not used in any method to determine the biological activity of SEQ ID NO:12, and as such one skilled in the art would not know how to determine a "biologically active" polypeptide" (Office Action, page 13). Applicants respectfully disagree. The specification describes, for example, a cell proliferation assay that uses mouse 3T3 fibroblasts (Specification at page 54, lines 7-15. The use of mouse 3T3 fibroblast in cell proliferation assays and tumorigenicity assays was well known in the art at the time of filing of the instant

application, and cell proliferation assays similar to the one described in the application have been used to identify oncogenes, including the Tre oncogene (Janssen et al. (1999) Int. J. Cancer 80:857-862). In fact, cell proliferation assays using mouse 3T3 fibroblasts have been used successfully with both Tre and PRC17 to detect oncogenic activity (See Pei et al., supra, pp. 5420-5421; Nakamura et al. (1992) Oncogene 7:733-741 (IDS reference No. 4); and Janssen et al., supra, p. 857). Therefore, one of skill in the art could readily use mouse 3T3 fibroblasts in assays of the SEQ ID NO:12 polypeptide to detect cell proliferative activity without undue experimentation.

The Examiner has cited some references (Burgess et al. (1990) J. Cell Biol. 111:2129-2138; Lazar et al. (1988) Mol. Cell. Biol. 8:1247-1252; Schwartz et al. (1987) Proc. Natl. Acad. Sci. U.S.A. 84:6408-6411; Lin et al. (1975) Biochemistry 14:1559-1563) that supposedly underscore the "unpredictability" of protein chemistry. Again, Applicants respectfully point out that the claims of the instant application are drawn to **naturally-occurring** variants. Thus it is not necessary to screen every conceivable variant which might be made using recombinant methods, as all that is claimed are those variant sequences which are found in nature. Through the process of natural selection, nature will have determined the appropriate sequences.

Furthermore, the claims are directed to polynucleotides, not polypeptides, and it is the functionality of the claimed polynucleotides, not the polypeptides encoded by them, that is relevant. Members of the claimed genus of variants may include, for example, mutant alleles associated with diseases, or single nucleotide polymorphisms (SNPs). Members of the claimed genus of variants may be useful even if they encode defective PROAP polypeptides. For example, the variant polynucleotides could be used for the detection of sequences related to PROAP (see the specification, for example, at page 30, lines 26-29, and page 42, lines 6-23) including PROAP variants that may be associated with disease states, such as the diseases listed on page 32, line 24 through page 33, line 17, of the specification. See the specification at, for example, pages 41-46 for disclosure of how to use the claimed sequences in diagnostic assays.

Contrary to the Examiner's assertions, immunogenic fragments of SEQ ID NO:12 are amply enabled by the disclosure of the specification. For example, at page, lines, the specification describes methods for identifying immunogenic fragments.

> Alternatively, the PROAP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means

known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)
(Specification at page 56, lines 26-30)

The specification further describes the use of immunogenic fragments to induce antibodies that bind specifically to a given region of a protein.

> When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.
> (Specification at page 11, lines 20-24)

At page 31, lines 17-19, the specification states:

> For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with PROAP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable. (Specification at page 34, lines 17-23)

The specification continues at page 56, line 31 through page 57, line 3 with a description of the immunogenic fragments that could be used to induce antibodies:

> Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-PROAP activity by, for example, binding the peptide or PROAP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

Immunogenic fragments of SEQ ID NO:12 by definition elicit antibodies that bind to SEQ ID NO:12. It is routine to produce antibodies that specifically bind to a protein by immunizing an appropriate host with oligopeptide fragments of a protein. It is well known in the art that it is possible to produce antibodies to almost any part of an antigen. Given the sequence of SEQ ID NO:12, one of skill in the art could readily identify immunogenic fragments of SEQ ID NO:12.

The Examiner's greatly exaggerates the difficulty of identifying immunogenic fragments that would elicit antibodies capable of specifically bind to PROAP or variants thereof. One of skill in the art can routinely produce antibodies that specifically bind to a protein by immunizing an appropiate host with oligopeptide fragments of that protein. It is well known in the art that it is possible to produce antibodies to almost any part of an antigen, and is not especially difficult to obtain antibodies with specificity for a protein. In fact, one of skill in the art can routinely obtain specific antibodies, and the specification describes various methods for identifying antibodies with specificity for proteins having the sequences of SEQ ID NO:12 or variants or fragments thereof.

In general, antibody production is an empiric process that necessarily requires immunization with particular putative immunogenic fragments and subsequent screening of the products (e.g. antisera, hybridoma supernatants, recombinant immunoglobulin libraries or panels of highly specific binding reagents) to identify those fragments capable of giving rise to antibodies having the requisite specificity and affinity for the target antigen (in the present case, SEQ ID NO:12). This procedure is routine in the art, and does not constitute undue experimentation which would render Applicants' invention not enabled. See, e.g., *In re Wands* 8USPQ 2d 1400 (CAFC 1988). Indeed, the generation of antibodies necessarily involves genetic rearrangement in reaction to immunogenic challenge; that rearrangement process, and the resulting products, are inherently variable and constitute the basis for the remarkable ability of the mammalian immune system to respond to novel antigenic challenges with a high degree of specificity. Therefore, the process of challenge and screening are an inherent and unavoidable part of identifying immunogenic fragments, and cannot be considered undue experimentation.

Further, the Examiner requires working examples (Office Action, page 4). There is no such requirement under the law to provide "working examples." As set forth in *In re Borkowski,* 164 USPQ 642, 645 (CCPA 1970) (footnote omitted):

> However, as we have stated in a number of opinions, a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

See also M.P.E.P. 2164.02 as follows:

> Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic"... A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

Thus, there is no requirement under the law to provide "working examples" of what is claimed. Rather, one looks to whether the specification provides a description of how to make what is claimed. The present specification provides the requisite description.

Contrary to the standard set forth in *Marzocchi* and *Borkowski*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present specification would enable one to make and use the recited polynucleotides. Hence, a *prima facie* case for non-enablement has not been established. For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: November 3, 2003

Jenny Buchbinder
Reg. No. 48,588
Direct Dial Telephone: (650) 843-7212

Date: November 3, 2003

James M. Verna, Ph.D.
Reg. No. 33,287
Direct Dial Telephone: (650) 845 -5415

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Enclosures:

1. Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, Xenobiotica 29:655-691 (1999).
2. Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proc. Nat. Acad. Sci. 94:8945-8947 (1997).

3. Emile F. Nuwaysir et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999).
4. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000).
5. John C. Rockett and David J. Dix, Application of DNA arrays to toxicology, 107 Environ. Health Perspec. 107:681-685 (1999).
6. Email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding.
7. Brenner et al., Proc. Natl. Acad. Sci. 95:6073-6078 (1998).
8. Pei et al Cancer Res. 62:5420-5424) (2002).
9. Martinu et al. J. Biol. Chem. 277:50996-51002 (2002).
10. Masuda-Robens et al. Mol. Cell. Biol. 23:2151-2161 (2003).
11. Janssen et al. Int. J. Cancer 80:857-862 (1999).
12. Exhibit A
13. Exhibit B